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| EXAMINER | |
|---|---|
| OLSEN, KAJ K | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/556,910 | RYLATT ET AL. | |
| | Examiner | Art Unit | |
| | KAJ K. OLSEN | 1795 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

3. Claims 2 and 3 are drawn to the use of the claimed cell separation process for a number of specific types of cells. However, except for erythrocytes and leukocytes, applicant has not enabled one of ordinary skill in the art to extend the claimed process to any of the other identified cells of these claims. In particular, applicant only demonstrated the use of this process for separation of red and white blood cells and appeared to rely on the fact that these two types of cells have sufficient charge to induce useful electrophoretic movement and have different ranges of sizes allowing one to separate them from each other by size exclusion (specification p. 10, ll. 3 and 4). This would clearly not be universal phenomenon automatically applicable to other cell types and more than routine skill in the art would be necessary to extend this device to these other types of cells being explicitly claimed. Applicant has not demonstrated for any of these other types of cells that similar conditions can be established. One possessing ordinary skill in the art would not have been enabled to utilize the claimed invention for these other specific cells of claims 2 and 3.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-10, 12, 14, 15, 18-28, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Egen et al (USP 5,336,387) with or without the further teaching of O'Farrell (USP 4,323,439). Egen and O'Farrell are being cited and relied on for the first time with this office action.

7. With respect to claim 1, Egen discloses a process for separating a cell type from a mixture of cell types by electrophoresis comprising providing a device having a number of sample chambers 12 that would read on the defined first and second sample chambers, and first and second electrolyte chambers (30, 32). All the various sample chambers are between the first and second electrolyte chambers with membrane barriers 17 separating the first and second

sample chambers (i.e. the first barrier). Furthermore the membrane barriers 17 on the very end of the device separate the electrolyte chambers from any of the first and second sample chambers. Egen further discloses the presence of electrodes in the first and second electrolyte chambers. See fig. 6 and 11 and col. 5, ll. 11-54. With respect to the barriers 17 being ion permeable, because these barriers allow fluid transport as well as electrical field transport, they are clearly ion permeable barriers. Egen discloses an embodiment where an electric potential is applied to a mixture of cells in a sample chamber (chamber 5 in the examples) to control the sample migration across the various ion permeable barriers. See col. 16, l. 33 - col. 17, l. 41. Although Egen does not specify the particular concentration of cells being separated, it would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize Egen with $10^5$ to $10^{10}$ cells/mL in order to maximize the yield of separated cells. It is unclear from Egen whether the primary sample flow from compartment 5 towards compartments 6-9 is due to the electrophoresis or due to the counter flow. If the electrophoretic flow controls, then the movement of the cells from compartment 5 into compartments 6-9 clearly reads on limitation b of claim 1. If the counter flow is the primary motive means, then the electrical field is being primarily used to impede the fluid flow and isn't actually inducing most of the cellular movement across the ion permeable barriers. However even in this case, Table 5 shows that some of the sheep red blood cells that started in chamber 5 ended up in chamber 4 indicating that for some of the sheep red blood cells, the electric field would have been a more powerful sample motive means than the counter flow (i.e. these samples moved against the counter flow). This sample movement would read on limitation b of claim 1.

8. Alternatively, Egen derived its counter flow concept from O'Farrell (col. 11, ll. 41-56). O'Farrell teaches that one can utilize a counter flow that is stronger than the electrophoretic flow or one can utilize an electrophoretic flow that is stronger. See col. 5, ll. 28-38. Hence, even if Egen relied on the counter flow to do most of the fluid movement, it would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the suggestion of O'Farrell and rely on an electrophoretic flow that is stronger than the counter flow as both would be capable of providing the desired separation between the cells. Even Egen col. 11, l. 60 – col. 12, l. 9 suggests that the electrophoretic force is the primary motive means.

9. With respect to claims 2 and 3, red blood cells are erythrocytes.

10. With respect to claim 4, sheep and rabbit blood cells (or healthy and infected blood cells) constitute two different cell populations.

11. With respect to claim 5, whether or not sheep or rabbit blood cells (or healthy or infected blood cells) are wanted or unwanted completely depends on the unspecified and unclaimed use of the process. Because the process of Egen can be utilized to separate wanted cells from unwanted cells, it meets the claim.

12. With respect to claim 6, because the electrophoresis of Egen is being utilized as the primary motive means to move the sample (with only the counter flow counteracting that primary flow) (see the discussion of Egen or Egen in view of O'Farrell above), then substantially all the migration of the sample would be due to the electric potential.

13. With respect to claim 7, see Egen col. 5, ll. 47-54.

14. With respect to claim 8, Table 5 of Egen clearly shows that one applies the electric potential long enough to get the desired purity level.

15. With respect to claims 9 and 10, any membrane (i.e. ion permeable barrier) inherently has a characteristic average pore size and pore sized distribution. Moreover, Egen established that the pore size is critical to successful operation of the device (col. 17, ll. 29-41).

16. With respect to claim 12, Egen teaches the use of nylons and polypropylenes and teaches the use of pores large enough to permit cellular flow (col. 17, ll. 29-41).

17. With respect to claims 14 and 15, because Egen discloses that the pore size should be comparable to the size of the cells being separated (col. 17, ll. 29-41) and because cell can be in the range of 0.01-100 microns or 1-10 microns, it would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize pore sizes in these claimed ranges when the cells being separated have sizes in these claimed ranges.

18. With respect to claims 18, 19, and 21, because Egen is relying on electric field based separation of cells with voltages overlapping those of the present invention (compare col. 15, l. 23 and 24 with claim 21), greater than 50% or 60% of the cells should be viable or unchanged after separation.

19. With respect to claim 20, see Egen abstract.

20. With respect to claim 22, Egen disclosed no criticality to its use of 100-200 V. Moreover, Egen would not have needed this much voltage if the device were to be operated with fewer compartments. Hence, it would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize about 60 V if one wanted to utilize a voltage that would better protect the viability of the cells or if one wanted to utilize much less that 10 compartments.

21. With respect to claim 23 and 24, Egen teaches the use of 10 compartments (col. 16, ll. 33-37) where each compartment is between 0.1 to 0.4 cm thick (col. 6, ll. 17-21) and teaches the use of 100-200 V across the electrodes (col. 15, l. 22). This would overlap the claimed V/cm range of these claims. Finding the appropriate V/cm range to provide the desired electrophoretic movement without damaging the cells would have required only routine skill in the art.

22. With respect to claims 25 and 26, finding the amount of time necessary to arrive at the desired level of cell separation, including the use of 1-60 minutes or 10 minutes, would have required only routine skill in the art.

23. With respect to claim 27, the buffer constituents of Egen appear to be in the 100-400 mM range (col. 16, ll. 39-41). Alternatively, finding the appropriate buffer concentration that provides an effective electrophoretic medium while keeping the cells viable, including the use of 100-400 mM of concentration, requires only routine skill in the art.

24. With respect to claim 28, Egen uses both glucose and sucrose (col. 16, ll. 39-41).

25. With respect to claim 30, finding the concentration of cell mixture that can be effectively utilized with the device, including the use of $10^6$ to $10^8$ cells/mL, requires only routine skill in the art.

26. Claims 1-28, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prince et al (USP 6,491,819) in view of any one of Egen, Sammons et al (USP 5,906,724) or Ivory (USP 5,071,536) and Vigh et al (US 2002/0043465). Sammons, Ivory, and Vigh are being cited and relied on for the first time with this office action.

27. With respect to claim 1, Prince discloses a method of separating a cell type from a mixture of cell types that comprises providing a first membrane 100 separating a first chamber

from a second chamber (i.e. the upper and lower sides respectively of 100 in fig. 6 and 7) which allowed Prince to separate red blood cells from white blood cells. See col. 10, ll. 6-25. Prince further teaches that the flow parallel to the membranes with the addition of a perpendicular flow can be utilized to enhance the separation of the red blood cells from the white blood cells (col. 10, l. 25 – col. 11, l. 29). With respect to this membrane being ion permeable, a porous membrane would inherently be permeable to ion movement. Prince does not explicitly suggest the use of an electric field to induce that perpendicular cell flow. However, each of Egen, Sammons, and Ivory demonstrate that electrophoresis can be utilized as a means for inducing flow that is perpendicular to an overall sample flow with Egen and Sammons showing that electrophoresis can be utilized to drive a cellular flow across a membrane. In particular, the previously relied on Egen showed that electrophoresis can be utilized to generated cell flow through membranes that is perpendicular to the overall sample flow such that desired separation between the cells can be garnered. See the discussion above. Sammons is related to Egen (col. 2, ll. 6-12) and explicitly teaches that electrophoretic forces can be generated through membranes for the explicit purpose of separating white blood cells from red blood cells (col. 10, ll. 21-27). Ivory similarly shows that electrophoretic forces can be generated that are perpendicular to the sample flow in order to aid in the separation of a mixture of cells. See fig. 3a and 3b and col. 8, ll. 3-26 fig. 6A-6C. It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teachings of Egen, Sammons, or Ivory and rely on an electric field to generate a transverse force for Prince because the utility of one known means of inducing perpendicular movement for another means requires only routine skill in the art. For the use of the electrophoretic motion, Egen, Sammons, and Ivory all teach

the use of a pair of electrodes in first and second electrolyte chambers that would have to have the first and second sample chambers between them so as to generate the desired perpendicular electrophoretic force. As to the presence of second and third ion permeable barriers, none of Egen, Sammons, or Ivory explicitly discloses the presence of a barrier separating the electrolyte chambers from the sample chambers. However, Vigh teaches an alternate device for generating perpendicular electrophoretic movement and explicitly teaches the use of second and third ion permeable barriers to separate the electrolyte chambers from the sample chambers presumably to keep the sample constituents from reaching either the electrolyte chambers or the electrodes and to keep the electrolyte from mixing with the sample. See par. 0080 and 0081. It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teaching of Vigh for the process of Prince in view of Egen, Sammons, or Ivory so as to keep the sample constituents within the sample chambers and the electrolyte within the electrolyte chambers.

28. With respect to claim 2-4, Prince is separating erythrocytes from leukocytes, which are two cell populations.

29. With respect to claim 5, red blood cells are presumably a wanted type of cell that is passed through the ion barrier.

30. With respect to claim 6, Egen, Sammons, and Ivory rely on the electrophoretic force for the transbarrier migration.

31. With respect to claim 7, this is an inherent function of the use of ion permeable barriers. See Egen col. 5, ll. 47-54.

32. With respect to claim 8, it clearly would have been obvious to one of ordinary skill in the art to apply the potential long enough to generate the desired level of purity of sample.

33. With respect to claims 9-11 and 14-17, see Prince col. 7, ll. 34-39 and Vigh par. 0080 and 0081.

34. With respect to claims 12 and 13, see Prince col. 7, ll. 10-25.

35. With respect to claims 18 and 19, because Egen is relying on electric field based separation of cells with voltages overlapping those of the present invention (compare col. 15, l. 23 and 24 with claim 21), greater than 50% or 60% of the cells should be viable or unchanged after separation.

36. With respect to claim 20, both batch and continuous measurements are known separation schemes (see Egen abstract).

37. With respect to claim 21, see Egen col. 15, ll. 23 and 24.

38. With respect to claim 22, the choice of voltage is going to be a function of the desired V/cm of voltage applied times the total thickness of the two chambers. Because both Egen and Ivory suggest the use of voltages around 25 V/cm (see the discussion of claims 23 and 24 below), the use of about 60 V would have been obvious for a device having a total thickness of about 2.4 cm. Furthermore, there is no criticality suggested for the choices of voltages of Egen and Ivory finding a voltage that balances electrophoretic movement with cell viability, including the use of 60 V, would have required only routine skill in the art.

39. With respect to claim 23 and 24, see the discussion of Egen above. See also Ivory col. 8, l. 5. Finding the necessary V/cm to provide the desired electrophoretic movement without damaging the cells would have required only routine skill in the art.

40. With respect to claims 25 and 26, finding the amount of time necessary to arrive at the desired level of cell separation, including the use of 1-60 minutes or 10 minutes, would have required only routine skill in the art.

41. With respect to claim 27, the buffer constituents of Egen appear to be in the 100-400 mM range (col. 16, ll. 39-41). Alternatively, finding the appropriate buffer concentration that provides an effective electrophoretic medium while keeping the cells viable, including the use of 100-400 mM of concentration, requires only routine skill in the art.

42. With respect to claim 28, Egen uses both glucose and sucrose (col. 16, ll. 39-41).

43. With respect to claim 30, finding the concentration of cell mixture that can be effectively utilized with the device, including the use of $10^6$ to $10^8$ cells/mL, requires only routine skill in the art.

44. Claims 11, 16, and 17 (and claim 1 in the alterative) are rejected under 35 U.S.C. 103(a) as being unpatentable over Egen with or without O'Farrell in further view of Vigh.

45. With respect to claim 11, Egen set forth all the limitations of the claim, but did not explicitly disclose that at least a portion of the membranes are made from polyacrylamide with a 5 kDa mass cut-off. Vigh teaches that between the electrolyte compartments and the sample chambers, one should include restriction membranes having a mass cut off of 5 kDa. See par. 0080. It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teaching of Vigh for the process of Egen so that the electrolyte chambers and the end sample chambers do not get mixed together. Furthermore, a restriction membrane will keep sample constituents from being driven all the way to the electrodes.

46. With respect to claims 16 and 17 (those limitations not covered above), Egen already disclosed that the membranes between the sample chamber need to be on the scale of the cells being passed (col. 17, ll. 29-41), the second and third ion permeable barriers of Vigh would clearly have a molecular mass cut off much less than the cut off for the membranes between the sample chambers.

47. With respect to claim 1 in the alternative, in the rejection above, the examiner read the additional membranes 17 near the end compartments as reading on the defined ion permeable barriers even though it is not clear if there are any membranes directly separating the electrolyte chambers from these end sample chambers. Even if the examiner read the claimed second and third ion permeable barriers as being directly between the electrolyte chambers and any sample chambers, then the use of second and third ion permeable barrier would have been further obvious over the teaching of Vigh for the reasons set forth for claim 11 above.

48. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Egen with or without O'Farrell in further view of Prince.

49. Egen set forth all the limitations of the claim, but did not disclose the use of a polycarbonate membrane. Prince discloses that polycarbonate is a known form of cell permeable membranes (see col. 7, ll. 10-25). It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teaching of Prince for the membrane of Egen because the substitution of one known membrane for another known membrane requires only routine skill in the art.

### *Response to Arguments*

50. Applicant's arguments filed 3/1/2010, with respect to the rejections by the previous examiner have been fully considered and are persuasive. Therefore, the rejection has been withdrawn and a new grounds of rejection is being introduced here.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAJ K. OLSEN whose telephone number is (571)272-1344. The examiner can normally be reached on M-F 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam X. Nguyen can be reached on 571-272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kaj K Olsen/
Primary Examiner, Art Unit 1795

May 13, 2010